AMENDMENTS TO THE DRAWINGS:

Please amend the drawings according to the attached Figures, on which the amendments are indicated in red ink. Specifically, in Figure 6, please label the left frame "A" and the right frame "B". The attached sheet, which includes Figure 6, replaces the original sheet of drawings for Figure 6.

Attachments following last page of this Amendment:

Replacement Sheet (1 page)
Annotated Sheet Showing Change(s) (1 page)

REMARKS

A check for the fees for a three month extension of time accompanies this response. Any fees that may be due in connection with filing this paper or with this application during its entire pendency may be charged to Deposit Account No. 06-1050. If a Petition for extension of time is required, this paper is to be considered such Petition, and any fee charged to Deposit Account No. 06-1050. A Supplemental Information Disclosure Statement is being filed on the same day herewith, under separate cover.

Amendments to the Specification

An amendment to the specification is made for clarity. The description for Figure 7 in the paragraph beginning at page 5, line 29, describes panels (A-C) as specimens from catheterized rats. It is implicit in the description that the remaining panels, (A'-C'), describe corresponding specimens from the control animals (*i.e.*, A' corresponds to A; B' corresponds to B; and C' corresponds to C).

For example, the description for Figure 7 states that "in the control animals, bacteria were detected in the liver (A) and spleen (B) but not the heart (C)." The cited phrase is consistent with the graphic representation of the results shown in "specimen" panels (A-C) and corresponding "control" panels (A'-C') of Figure 7. Further, the identity of the specimens for each column is described in the description for Figure 7, where (A) describes liver specimens, (B) describes spleen specimens, and (C) describes heart specimens. The specification therefore has been amended to point to the panels describing the control animals (A'-C') in an explicit fashion and thereby clarify the description. No new matter is added.

Amendments to the Drawings

The amendment to the drawings corrects a typographical error and further provides clarity. The amendment to Figure 6 labels the first frame "A" and the second frame "B" (beginning from the left under the heading, "Figure 6."). Basis for this amendment can be found in the specification, for example, at page 17, line 31 to page 18, line 1, which describes that the catheterized animals demonstrated colonization of the heart with light-emitting bacteria, while the control animals did not. The frame on the right clearly demonstrates the described colonization with visualization of light. Further, the description of Figure 6 beginning at page 5, line 19, describes that the colonization of the heart with light-emitting bacteria in catheterized rats is depicted in B, while the control frame is A. The frames therefore are explicitly labeled accordingly. No new matter is added.

Amendments to the Claims

Claims 33-47 and 51-79 are pending in this application. These claims are set forth in the Listing of Claims above, which replaces all prior versions and listings of claims in the application. Claims 33-35 are amended herein to clarify the nature of what is claimed. Claims 48-50 are cancelled. The amendments to Claims 33-35 find basis in the specification, for example, at page 3, lines 23-26; at page 6, line 31 to page 7, line 4; and at page 7, lines 28-31; at page 12, paragraph 0046 and in Claim 21 as originally filed. No new matter is added.

Claim 80 is added herein. Basis for added Claim 80 can be found in the specification, for example, at page 12, paragraph 0046. No new matter is added.

I. OBJECTIONS TO THE DRAWINGS

Drawing 6 is objected to as having two panels that are referred to as panels A and B in the specification, but are not marked as such in the drawing. Drawing 6 has been amended to designate the panels as described in the specification, thereby obviating this rejection. As explained in the "Remarks" section above, no new matter is added by this amendment.

Drawing 7 is objected to because it allegedly is not clear which of the panels refer to heart, liver or spleen, and further which panels are control or catheterized animals. The description of Figure 7 at page 5, paragraph 0022, has been amended herein to explicitly point to the control panels *vs.* the catheterized animal panels in Figure 7. The description further notes which of the panels refer to heart, liver or spleen. As explained in the "Remarks" section above, no new matter is added by this amendment.

II. OBJECTION TO CLAIMS 61-63 UNDER 37 CFR §1.75(c)

Claims 61-63 are objected to under 37 CFR §1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of a previous claim. Specifically, it is alleged that the phrase "detection is based on a signal" does not further limit the base claim because all detection is based on some form of signal. This objection respectfully is traversed.

First, it respectfully is submitted that the test for proper dependence is not whether a claim further limits a base claim, but whether a dependent claim includes all limitations of the

base claim (*see e.g.*, 35 U.S.C. §112, fourth paragraph). In this instance, Claims 61-63 each include all limitations of their respective base claims, 33-35.

It also is submitted that, contrary to the Examiner's assertion, not all detection is based on a signal. As is known to those of skill in the art, a signal is an indirect indicator or measurement of the object or property of interest. For example, Merriam Webster's Collegiate Dictionary (Tenth Edition, 1993) defines a signal as "something that conveys notice." Thus, a signal is indicative that an object or property of interest is present, but is not a direct measurement of the object or property itself. Detection can be direct, *e.g.*, an observation of the actual object (microorganism or cell, in this instance), or it can be indirect by means of a signal, such as light, fluorescence or MRI, suggesting the existence of a microorganism without seeing the microorganism itself. Applicant therefore respectfully submits that detection by means of a signal is a further limitation of detection *per se*.

The description in the specification is consistent with what is understood by those of skill in the art as a signal. There are descriptions throughout the specification distinguishing detection *per se* from detection by means of a signal. For example, at page 3, paragraph 0009, the specification describes how sites of inflammation can be visualized by detecting bacterial colonization. It was known to those of skill in the art as of this application's earliest priority date that cells and microorganisms, such as bacteria and bacterial colonies, are objects that can be visualized directly and therefore detected directly by means of, for example, electron micrographs or microscopy (*see, e.g.*, Lemmon *et al.*, *Gene Therapy*, 4:791-796 (1997); of record as Item DI an IDS filed February 17, 2005, in connection with the above-captioned application). The same paragraph then states that the expression of genes encoding light-emitting proteins in bacteria and measurement of light is a non-invasive way to trace bacteria in a living host, *i.e.*, the light *signal* indicates the presence of bacteria but it is not a *direct* detection of the bacteria themselves.

The specification at page 6, paragraph 0023, describes how initial experiments with the bacterium *S. typhimurium* showed that tissues irritated by implanted materials such as sutures and prosthetic devices are susceptible to colonization by the bacteria. The same paragraph then goes on to say that the observation of these bacterial colonies formed the basis for designing microorganisms and cells whose detection is *"based on signals"* (emphasis added). The specification clearly states that while in some embodiments, the microorganism or cell can be engineered for indirect detection by means of a signal, such as luminescence,

fluorescence or MRI (*see, e.g.*, page 8, paragraphs 0028 and 0029), *any* non-pathogenic or attenuated microorganism or cell is useful for practicing the instant methods (*see, e.g.*, page 7, paragraph 0027.

The specification at page 6, paragraph 0024 and at page 7, paragraph 0025, further distinguishes types of detection by describing that the methods can be performed using a microorganism or cell "encoding a detectable protein *or a protein capable of inducing a detectable signal*" (emphasis added). also describes how the microorganism or cell detection based on a signal is a further limitation of detection *per se*.

In light of the above, Applicant respectfully submits that Claims 61-63 are not in improper dependent form and do specify a further limitation of their respective base claims.

III. PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTION OVER U.S. PATENT APPLICATION NO. 10/516,785

Claims 33-79 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over Claims 1 and 3-19 of copending U.S. Application Serial No. 10/516,785. Because it is not clear at this point (i) which of the above applications will issue first, if at all, and (ii) what the scope of the allowed claims in each application will be, Applicant respectfully requests either reconsideration and withdrawal of this provisional rejection, or deferral of the ground of rejection until such time as the issue is ripe.

IV. REJECTION OF CLAIMS 61-63 UNDER 35 U.S.C. §101 FOR STATUTORY-TYPE DOUBLE-PATENTING

Claims 61, 62 and 63 are rejected under 35 U.S.C. §101 statutory-type double patenting as allegedly coextensive in scope with their respective base Claims 33, 34 and 35. Specifically, it is alleged that the rejected claims are "substantial duplicates" of the base claims because the recitation of detection by a signal does not further limit detection because "all detections are based on signals."

This rejection respectfully is traversed. It respectfully is submitted that Claims 61-63, which specify the limitation that detection is "based on a signal," render these claims of different scope and not identical or substantially duplicative with their respective base claims 33-35. As discussed above in addressing the objection to Claims 61-63 under 37 CFR §1.75(c), detection by a signal is distinguishable from detection *per se*. Microrganisms and

cells can be visualized directly, such as by electron micrograph, or they can be engineered to emit a signal, such as light, which then can be measured as indicative of the presence of the microorganism or cell. When the presence of an object or a property of interest is indicated by a signal, the detection is indirect. There is notice that the object or property exists, but the actual object or property has not been detected.

In the instant application, when detection is by means of a signal, one is not directly seeing the microorganism or cell, but instead is measuring a light emission, magnetic resonance, or other such signal that indicates the microorganism or cell is present. Therefore, Applicant respectfully submits that the limitation in Claims 61-63 that recites detection by means of a signal renders these claims of different scope and not duplicative with their respective base claims

V. REJECTIONS OF CLAIMS 33-79 UNDER 35 U.S.C. §112, FIRST PARAGRAPH – NEW MATTER AND WRITTEN DESCRIPTION

Claims 33-79 are rejected under 35 U.S.C. §112, first paragraph, as lacking adequate written description and/or containing new matter. Various grounds of rejection are set forth, each of which are addressed in turn below.

1) Claims 33-79 are rejected as containing new matter because there allegedly is no basis for the recitation of two disconnected steps, one for the administration and detection of microorganisms or cells, the other for the detection of wounds or wounded tissues, with no nexus between the steps. The claims are amended herein to specify a nexus clarifying that detection of the microorganism or cell permits detection of the wound or wounded tissue. Accordingly, reconsideration and withdrawal of this rejection respectfully is requested.

2) Claims 35, 38, 39, 44, 47, 50, 53, 56, 63, 66, 73, 76 and 79 are rejected as containing new matter. Specifically, it is alleged that there is no basis for claims that recite diagnosis of low back pain *and* herniated nucleus pulposis because the specification and claims as originally filed allegedly only provide support for herniated nucleus pulposis *being* low back pain. Without addressing the merits of the rejection, in the interest of advancing prosecution, Claim 35 is amended herein to delete the phrase "herniated nucleus pulposis" and include it in dependent Claim 80, which specifies forms of inflammatory bowel disease and low back pain.

3) Claims 33-79 are rejected for failing to comply with the written description requirement because there allegedly is inadequate written description for claims that encompass pathogenic organisms and microorganisms that are not recognized by the immune system. This rejection is rendered moot by amendment of the claims to specify that the microorganism or cell is non-pathogenic or attenuated and is recognized by the immune system of the subject.

New Matter/Written Description Rejections that are Traversed

4) Claims 35, 38, 39, 44, 47, 50, 53, 56, 63, 66, 73, 76 and 79 are rejected as lacking adequate written description because the claims encompass diagnosis and treatment and the specification allegedly only describes the treatment and not the diagnosis of Crohn's disease, ulcerative colitis, atherosclerotic plaque, auto-immune disease, rheumatoid arthritis, multiple sclerosis, Alzheimer's disease, a fracture, an incision and a burn.

5) Claims 33-79 are rejected as containing new matter in their inclusion of methods wherein the microorganism or cell does not contain a DNA sequence encoding a protein capable of inducing a detectable signal.

These rejections respectfully are traversed.

Relevant Law

The purpose behind the written description requirement is to ensure that the patent applicant had possession of the claimed subject matter at the time of filing of the application *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific

compound [claimed embodiment] *Vas-Cath, Inc. v. Mahurkar*, at 1115, quoting *In re Ruschig*, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir. 1989).

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also Ex parte Sorenson*, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a parent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. *In re Reynolds*, 443, F.2d 384, 170 USPQ 94 (CCPA 1971); and *In re Smythe*, 480 F.2d 1376, 178 USPQ 279 (CCPA 1973).

Furthermore, the subject matter of the claims need not be described literally (*i.e.* using the same terms or *inhaec verba*) in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed

subject matter is not described in that application. This conclusion will result in the rejection of the claims affected under 35 U.S.C. 112, first paragraph – description requirement, or denial of the benefit of the filing date of a previously filed application, as appropriate.

Analysis

4) Traversal of the rejection of Claims 35, 38, 39, 44, 47, 50, 53, 56, 63, 66, 73, 76 and 79 as satisfying the written description requirement only for treatment and not for diagnosis of diseases.

It respectfully is submitted that the specification adequately describes the claimed methods for diagnosis as well as treatment of diseases. As the specification describes, for example, at pages 6 and 7, paragraphs 0023 and 0024, the instant methods are premised on the ability to direct cells and microorganisms to sites of disease, inflammation or injury, then detect the cells or microorganisms that have accumulated at these sites. The cells or microorganisms serve as tools to detect a wounded or diseased or inflamed site, which then can be treated. What is treated is what is detected or diagnosed, using suitable cells or microorganisms in the methods as described in the specification and claimed herein. The cells or microorganisms hone in on diseased or damaged sites. The methods described herein use these cells or microorganisms, therefore diagnosis necessarily occurs as the methods are based on tracking where the microorganisms or cells localize. As described extensively throughout the specification, treatment then can be administered either using an independent therapeutic agent or by modifying the microorganism or cell to contain a therapeutic agent.

As the Examiner has acknowledged, Applicant had possession of the claimed subject matter for the treatment of various diseases. Therefore, Applicant had possession of the claimed subject matter for the diagnosis of these diseases because they were diagnosed before they were treated, using the methods as claimed. The specification describes in great detail how to administer cells or microorganisms to subjects, detect sites of accumulation including diseased or wounded sites, then treat the sites of accumulation.

Thus, for example, paragraph 0024 beginning at page 6 of the specification describes how a microorganism or cell containing a detectable protein or a protein capable of inducing a detectable signal can be used for diagnosis and/or visualization of wounded or inflamed tissue, or an associated disease state. The paragraph then goes on to describe that following visualization, compounds suitable for therapy can be applied.

The specification, beginning at page 12, paragraph 0046, to page 14, paragraph 0049 goes on to describe exemplary diseases that can be diagnosed and treated using the microrganisms and cells as described. The specification at page 13, paragraph 0047, exemplifies how atherosclerotic plaques are imaged by targeting microorganisms or cells to the plaques, then treated by standard therapies or by modifying the microorganisms or cells to include a therapeutic agent, such as a plaque-destroying enzyme. Each of the therapeutic applications described in the aforementioned sections of the specification use microorganisms and cells that hone in on and accumulate at diseased or damaged sites. It is this "tracking," *i.e.*, diagnosis, that is used to identify sites of treatment.

It is noted that the subject matter of the claims need not be described literally (*i.e.* using the same terms or *inhaec verba*) in order for the disclosure to satisfy the written description requirement. The specification describes how microorganisms and cells can be used to hone in on diseased sites. The specification further describes diseases that can be treated using these cells and microorganisms. It is implicit that the diseased sites are identified/diagnosed using the cells and microorganisms, as that is their property.

The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (*see also*, MPEP 2163.02). It respectfully is submitted that Applicant clearly had possession of the instant methods for the detection/diagnosis of diseases because the subject matter is premised on the ability of administered microorganisms and cells to be traceable to sites of disease, which then are identified and diagnosed. There is no treatment without first locating the site of treatment, and location of the site of treatment and identification of the disease inherently occurs when the microorganisms and cells are used as described throughout the specification. Therefore, Applicant respectfully submits that the instant claims for the detection of various recited diseases are adequately supported by written description.

5) Traversal of the rejection of Claims 33-79 as containing new matter in their inclusion of methods that recite microorganisms or cells that do not encode a protein capable of inducing a detectable signal.

It respectfully is submitted that there is adequate basis in the specification for microorganisms or cells that do not encode a protein capable of inducing a detectable signal. As the specification describes, for example, at page 6, paragraph 0023, Applicant observed that wounded or inflamed tissue was susceptible to colonization by bacteria that honed in on the site of the wound or inflammation. This observation was used to design microorganisms whose localization could be traced based on signals, such as light emission or MRI. No signal is necessary to localize and/or visualize the microorganism or cell, it is one embodiment of the method.

Further, even when a signal is present, it need not come from a protein that is encoded by the microorganism or cell. The specification clearly describes that the microorganisms or cells used in the instant methods can "encode a detectable protein *or* a protein capable of inducing a detectable signal." (*see, e.g.*, page 6, paragraph 0024, and page 7, paragraph 0025). As the specification describes, for example, at page 8, paragraph 0029, a detectable protein in the microorganism or cell can bind a signaling moiety, such as a contrasting agent, chromophore, or compound required for visualization of tissues. The protein is not required to be capable of inducing a detectable signal. Thus, it respectfully is submitted that the inclusion of microorganisms and cells other than those that encode a protein capable of inducing a detectable signal, does not constitute new matter.

VI. REJECTION OF CLAIMS 33-79 UNDER 35 U.S.C. §112, FIRST PARAGRAPH - ENABLEMENT

Claims 33-79 are rejected under 35 U.S.C. §112, first paragraph, for alleged inadequate scope of enablement. In particular, it is alleged that the claims are broad in their recitation of a wide variety of subjects, tissues, diseases, cells, microorganisms and detection methods, and that the teachings of the specification and working examples are insufficient to practice the breadth of the embodiments encompassed by the claims. Reconsideration of the grounds for this rejection is respectfully requested in view of the amendments herein and the following remarks.

Relevant law

To satisfy the enablement requirement of 35 U.S.C. §112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. *Atlas Powder Co. v. E.I. DuPont de Nemours*, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything within the scope of a broad claim." *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of §112, first paragraph "can be fulfilled by the use of illustrative examples or by broad terminology." *In re Marzocci et al.*, 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." *In re Grimme, Keil and Schmitz*, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. *Smith v. Snow*, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the subject matter *as claimed*. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability

of the art, and the breadth of the claims. *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

Summary of Arguments

A consideration of the factors enumerated in *In re Wands*, including the scope of the claims, the extensive teachings and examples in the specification for selecting, administering, and detecting microorganisms and cells, the high level of skill of those in this art, the advanced knowledge of those of skill in the art, the fact that it is predictable given the extensive teachings of the instant application and the state of the art at the time of the effective date of the claims, it would not require undue experimentation for one of skill in the art to practice the methods as claimed herein to introduce any detectable microorganism or cell into a subject for the detection of a wound, wounded tissue, inflammation, inflamed tissue, or disease or condition associated thereof. The instant claims are directed to methods that include the steps of introducing a detectable microorganism or cell to a subject, monitoring a subject to whom a detectable microorganism or cell has been administered for detection of the microorganism or cell, and detecting the presence or absence of the detectable microorganism or cell, thereby detecting the presence or absence of a wound, wounded tissue, inflammation, inflamed tissue, or disease or condition associated thereof. The steps of the methods claimed herein, including selection of a microorganism or cell, administration of the microorganism or cell to a subject, and detection of the microorganism or cell in the subject are all taught by the specification and include working examples to illustrate how to practice the claimed methods. The specification further teaches and exemplifies how a variety of microorganism or cells, including viruses, bacteria, and mammalian cells, can be used in the claimed methods for the detection of a variety of wounds, wounded tissues, inflammation, inflamed tissues, or diseases or conditions associated with wounds, wounded tissues, inflammation, or inflamed tissues.

1. Breadth of the claims

Applicant's independent claims are drawn to a method of detecting the presence or absence of a wound or wounded tissue (claim 33), inflammation site or inflamed tissue (claim 34), or a disease or condition (claim 35) in a subject. Each of claims 33, 34, and 35 requires monitoring a subject to whom any detectable non-pathogenic or attenuated microorganism or cell recognized by the immune system has been administered, for detecting the presence or

absence of the microorganism or cell, thereby detecting the wound, wounded tissue, inflammation site, inflamed tissue, or a disease or condition, in the same subject. Diseases and conditions for detection are included in claim 35 and are selected from among endocarditis, pericarditis, inflammatory bowel disease, low back pain, temporal arteritis, polyarteritis nodosa, an arthritic disease, atherosclerotic plaque, coronary artery disease, peripheral vascular disease, cerebral artery disease, auto-immune disease, rheumatoid arthritis, multiple sclerosis, Alzheimer's disease, a fracture, an incision and a burn. Dependent claim 39 recites that the condition selected is an atherosclerotic plaque.

Dependent claims encompass microorganisms or cells that are any bacteria (claims 36-38) or bacteria selected from four genera (*Salmonella*, *Vibrio*, *Listeria* and *Escherichia*) or four species (*Salmonella typhimurium*, *Vibrio cholerae*, *Listeria monocytogenes* and *Escherichia coli*) (claims 51-56). Additional dependent claims encompass microorganisms or cells that are administered intravenously (claims 45-47), microorganisms or cells that are capable of replicating (claims 42-44), and microorganisms or cells that are specifically retained at the wound, wounded tissue, inflammation site, or inflamed tissue due to protection from the immune system and further being cleared without affecting normal tissues (claims 40-41). Further dependent claims encompass microorganisms or cells that allow for visualization and external visualization of the wounded/inflamed tissues (claims 57-60), detection being based on a signal (claims 61-63), where the signal is detectable by magnetic resonance imaging (MRI; claims 64-66), microorganisms or cells that comprise a DNA encoding a contrasting agent, chromophore, compound, or ligand for visualization (claims 67-68), microorganisms or cells that allow for detection *via* light (claims 69-70), or microorganisms or cells that comprise a DNA encoding a fluorescent protein, luminescent protein, or metal binding protein (claims 71-73), luciferase and/or its substrate (claims 74-76), or GFP or RFP (claims 77-79). New claim 80 specifies that the disease or condition is Crohn's disease, ulcerative colitis or herniated nucleus pulposis

Applicant is entitled to claims that are commensurate in scope not only with what Applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicant has disclosed. In the instant application, Applicants disclose to the public methods and compositions for the detection of a wound, wounded tissue, an inflammation site, inflamed tissue, or a disease or condition associated thereof by administering and detecting a microorganism or cell that accumulates at

such sites. It is the Applicant's pioneering discovery that administered microorganisms and cells can hone in to and accumulate at sites of wounds or inflamed tissues without the addition of a targeting agent that led to the claimed method for using microorganisms and cells for detecting such sites and for treatment of the wounded or inflamed tissue where the microorganisms and cells localize. Hence, Applicants are entitled to claims that are broad in scope.

2. Level of Skill in the Art

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application, authored and reviewed by those known in the art, further evidences the high degree of skill in this art.

3. State of the Prior Art

At the time of filing of the application, a broad body of knowledge had amassed in the areas of microbiology, molecular biology, genetics, and medicine including many technical procedures covering the generation, preparation, administration and detection of bacteria, viruses, and cells, including production of recombinant organisms using recombinant nucleic acid techniques, and expression and detection of exemplary detectable proteins, which are employed in the claimed methods. Numerous such procedures are referenced in the instant application. For example:

- in paragraph [0032], the application references in vitro recombination techniques, synthetic methods and in vivo recombination methods as described in Sambrook et al., Molecular Cloning, A Laboratory Manual, 2nd edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y.

- in paragraph [0032], the application references luminescent or fluorescent proteins that can be used in the claimed methods including luciferase from *Vibrio harveyi* (Belas et al., Science 218 (1982), 791-793) and from *Vibrio fischerii* (Foran and Brown, Nucleic acids Res. 16 (1988), 177), firefly luciferase (de Wet et al., Mol. Cell. Biol. 7 (1987), 725-737), aequorin from *Aequorea victoria* (Prasher et al., Biochem. 26 (1987), 1326-1332), Renilla luciferase from *Renilla reniformis* (Lorenz et al., PNAS USA 88 (1991), 4438-4442) and green fluorescent protein from *Aequorea victoria* (Prasher et al., Gene 111 (1987), 229-233) have been described that allow the tracing of bacteria or viruses based on light emission. The

- in paragraph [0032], the application also reference exemplary techniques known in

the art for transformation and expression of these genes in bacteria allows detection of bacterial colonies with the aid of the low light imaging camera or individual bacteria under the fluorescent microscope (Engebrecht et al., Science 227 (1985), 1345-1347; Legocki et al., PNAS 83 (1986), 9080-9084; Chalfie et al., Science 263 (1994), 802-805).

- in paragraph [0034], the application provides examples in the Art for expression of luciferase genes in a variety of organisms and detection by low light imaging, including expression of luxAB in Rhizobia residing within the cytoplasm of cells of infected root nodules (Legocki et al., PNAS 83 (1986), 9080-9084; O'Kane et al., J. Plant Mol. Biol. 10 (1988), 387-399), Bacillus subtilis and Bacillus megatherium expression of lux A and lux B fusion genes (Fab2) in insect larvae and worms (Escher et al., PNAS 86 (1989), 6528-6532), Pseudomonas or Ervinia spp. expression of pathogen-activated PAL promoter-bacterial luciferase fusion gene in transgenic Arabidopsis plants, as well as in tomato plant and stacks of potatoes (Giacomin and Szalay, Plant Sci. 116 (1996), 59-72).

- in paragraph [0034], the application provides further references to techniques and methods for the use of the luxCDABE operon for expression of bacterial luciferase and administration methods for infecting mice with bacteria carrying the luxCDABE operon (Meighen and Szittner, J. Bacteriol. 174 (1992), 5371-5381, Lee et al., Eur. J. Biochem. 201 (1991), 161-167, Fernandez-Pinas and Wolk, Gene 150 (1994), 169-174, Contag et al., Mol. Microbiol. 18 (1995), 593-603).

- in paragraph [0062], the application references techniques, such as surgical heart defects, for the generation of mouse models of wounded/inflamed tissue for administering the microorganisms or cells (Santoro and Levison, Infect. Immun. 19(3) (1978), 915-918; Overholser et al., J. Infect. Dis. 155(1) (1987), 107-112).

Additional evidence to the state of the prior Art can also be found in the references made of record in the instant application. For example, art has been submitted by Applicant to the Patent Office in connection with the instant Application, which includes description of various methods of preparing, administering and detecting microorganisms and cells, including bacteria and viruses. A few illustrative examples of such references and review articles include Art which describes:

- additional techniques and methods for expression and detection of fluorescent and bioluminescent molecules as found in Belas et al., Science, 218: 791-793 (1982), Chalfie et al, Science 263: 802-805 (1994), Contag et al., Mol. Microbiol. 18: 593-603 (1995), Greer

III, L.F. and A.A. Szalay, Luminescence. 17(1):43-74 (2002), Rodriguez, J.F. et al., Proc. Natl. Acad. Sci. U.S.A., 85: 1667-1671 (1988), Rocchetta et al., Antimicrobial Agents and Chemotherapy 45(1): 129-137 (2001), Yang et al., PNAS 97(22): 12278-12282 (2000), Wang Y. et al., Mol Genet Genomics. 268(2):160-8 (2002), Lamberton et al., Proceedings of the 12th International Symposium on Bioluminescence & Chemiluminescence: 5-9 April 2002, Robinson College, University of Cambridge, UK, p 3.22 (2002)

- additional techniques and methods for use of other detectable molecules for *in vivo* labeling such as radionucleotides for MRI or PET imaging as found in Welling et al Eur J Nucl Med. 27(3):292-301 (2000), Adonai et al., Proc. Natl. Acad. Sci. USA 99: 3030-3035 (2002), Welling et al., Nucl Med Biol. 29(4):413-22 (2002), Nibbering et al., Nucl Med Commun. 19(12):1117-21 (1998), Weissleder, T. et al., Nat. Med. , 6(3): 351-354 (2000), Berger, F. and S.S. Gambhir, Breast Cancer Research 3: 28-35 (2001).

The references cited above are by no means an exhaustive list of the references that were available to one of skill in the art at the time filing. Instead, they are a representative selection of art to demonstrate the existence large volume of information regarding tested and reliable procedures available at the time of filing of the instant application and thus evidence the advanced state of the art at the relevant time.

a. Rebuttal to Examiner's argument that Yu et al. (2003) demonstrates that the Art is not enabling of the breadth of Applicant's claims

On Pages 11 and 12 of the Office Action, the Examiner alleges that Yu *et al.* demonstrates that bacteria, viruses or mammalian cells, when administered to subjects, accumulate in cancerous tissues, but not in any tissue recited in the claimed subject matter. The Examiner further alleges that Yu *et al.* teaches that the mechanism of bacterial colonization is unknown, that administration type-dependent colonization is common and that it is not "predictable" which administration will yield which colonization type.

First, it is noted that the test for enablement is whether the teachings of the *specification*, not the Art, allow one of skill in the art to practice the claimed subject matter with a reasonable, but not undue, amount of experimentation. Therefore, the Examiner's statement that Yu *et al.* is not enabling of the claimed subject matter, is inapt. Further, the cited reference, Yu *et al.* (2003) is a post filing-date reference and hence is not appropriate in a rejection on grounds of enablement. If the reference is applied to evidence a lack of operability, a rejection under 35 U.S.C. §101 should be set forth by the Examiner. Post-filing

date references can potentially be used to establish inoperability, though no such rejection has been set forth in the Office Action. The cited reference is irrelevant to whether or not the application teaches how to make and/or use the claimed method at the time the instant application was filed and as of its earliest priority date.

Furthermore, knowledge of the mechanism of colonization or colonization-type is irrelevant to the practice of the methods as claimed. By following the teachings of the specification, the microorganisms or cells can be administered and detected at a site of inflammation, irritation, wound or disease. The teachings of the specification, in light of the state of the art and the knowledge of those of skill in the art, allow one of skill in the art to practice the steps of the methods as claimed. Knowledge of the mechanism of localization of the microorganisms or cells, or the types of colonies visualized at the sites of localization, are irrelevant to the ability to localize and detect the microorganisms and cells as taught by the specification and claimed herein.

4. Nature of the Claimed Subject Matter

Applicant's claimed method is in the nature of detecting wounds, wounded tissues, inflammation, inflamed tissues, or diseases or conditions associated thereof by administration of any microorganism or cell and detecting their accumulation in the affected tissues. As taught by the specification, detecting the presence or absence of the administered microorganisms or cells thereby detects the presence or absence of the wounds, wounded tissues, inflammation, inflamed tissues, or diseases or conditions associated thereof.

a. Rebuttal to Examiner's assertion that the claims appear to require separate detection steps not taught by the specification

On page 11 of the Office action, the Examiner alleges:

> Applicant's claims appear to require separate detections of the microorganism or cell, and the tissue affected, and hence, there appears to be no direction and/or guidance for the presently claimed method. Hence, the Artisan would have to perform undue experimentation to determine the methods of detection, because the method of detection would not [be] reasonably predictable.

As discussed above, the claims are amended herein to clarify that detection of the microorganism or cell and detection of the affected tissue *do not* encompass two separate detection steps. The specification teaches that detecting the presence or absence of the detectable microorganism or cell, thereby allows detection the presence or absence of a wound or wounded tissue, an inflammation site or inflamed tissue, a disease or condition due

to accumulation of the microorganism or cell at such sites. Therefore, the detection of the affected tissue is not a separate detection step. Furthermore, the specification provides working examples (*see* below) of how to perform methods of detection and diagnosis of wounded, inflamed or diseased sites, based on detection of microorganisms or cells that are directed to and are localized at these sites.

5. Level of Predictability in the Art

In view of the level of skill in the art, the disclosure of the application, the knowledge of those of skill in the art, and the history of administration of microorganisms and cells to subjects for various therapeutic regimens, the level of predictability in the Art is high. A variety of non-pathogenic or attenuated microorganisms or cells that were available at the time of filing were routinely used for detection and treatment methods in diseases such as cancers. Selection of a particular microorganism or cell that can be administered to a subject would have been considered routine due to many years of documented experience in the art for the administration of various non-pathogenic or attenuated microorganisms or cells. Furthermore, one of skill in the art would have been familiar with methods to modify such organisms based on the teachings of the specification and what was known in the art.

Rebuttal to Examiner's argument that the Artisan would not reasonably predict that any microorganism would accumulate in any of the tissues claimed

On page 13 of the Office Action, the Examiner alleges:

> With regard to the microorganism which may be administered, the Artisan would not reasonably predict that any microorganism would accumulate in any of the tissues claimed. To wit, for example, a bacteriophage cannot even infect eukaryotic cells, and hence would not reasonably be predicted to accumulate anywhere except the liver.

The Examiner has not provided any evidence to support this assertion that a microorganism, such as a bacteriophage, would not, in fact, localize to a wound, wounded tissue, inflammation site or inflamed tissue. The Examiner cannot take judicial notice of such fact and should provide basis for such supposition. To the Applicant's knowledge, there is no evidence that bacteriophage do not accumulate in wounded or inflamed tissues. Nonetheless, the specification provides ample guidance and teachings for one of skill in the art to readily be able to administer a detectable microorganism, such as a bacteriophage, in order to detect its accumulation in a wound, wounded tissue, inflammation site or inflamed tissue. Hence, a

microorganism, such as a bacteriophage, can easily be employed by one of skill in the art for use in the claimed methods.

6. Amount of Direction and Guidance Provided by Applicant

The specification describes the generation, administration, and detection of microorganisms and cells for the detection of a wound, wounded tissue, an inflammation site, inflamed tissue, or a disease or condition associated thereof. The teachings of the specification describe how to select an organism or cell for use in the methods, how to administer the microorganism or cell, how to detect the microorganism or cell *in vivo*, and provides instruction on how to modify the microorganism or cell for diagnosis or therapy. The specification also provides guidance as to the selection of features of microorganisms or cells for use in the methods of detection (e.g., non-pathogenic or attenuated, recognition by the immune system). It is taught that such detection is useful for visualization of and diagnosis of the wounded or inflamed tissues and for therapy of the wounded or inflamed tissues, including identification of site for subsequent application of a therapeutic agent (paragraph [0024]) or directed expression of proteins suitable for therapy at the affected site.

The specification teaches examples of proteins that can be expressed by the microorganism or cell for diagnosis and treatment (paragraph [0025]). For example, diagnostic proteins, such as fluorescent, bioluminescent, and metal binding proteins (see, e.g., paragraphs [0029][0033]-[0037]) and therapeutic proteins, such as various growth factors and enzymes (see, e.g., paragraphs [0026]-[0037]) can be expressed by the microorganisms or cells and are described. Exemplary vectors including viral, mammalian, and bacterial vectors for the expression of such proteins are also exemplified (see, e.g., paragraphs [0023] and [0031]).

The specification teaches exemplary microorganisms and cells that can be used in the claimed methods including bacteria, such as attenuated *Salmonella typhimurium*, attenuated *Vibrio cholera*, attenuated *Listeria monocytogenec*, or *E. coli*, and viruses such as a Vaccinia virus, an adeno-associated virus (AAV), or a retrovirus (paragraph [0038]).

The specification further teaches methods of administering the microorganism or cell, including routes of administration and factors to be considered for assessing methods of administration and dosages (see, e.g., paragraph [0045] and the Examples). The specification also provides examples of diseases and conditions that are associated with wounded or inflamed tissue that can be used in the methods for diagnosis and treatment (see, e.g.,

paragraphs [0046]-[0048]). Also provided are examples of combination therapies that can be employed with the microorganisms or cells, including administration of therapeutic proteins and molecules (see, e.g., paragraph [0049]).

The specification provides additional exemplary uses of the administered microorganisms or cells including monitoring the efficacy of an antibiotic regimen or the resistance of various sutures and implantable materials to bacterial colonization (see, e.g., paragraph [0050].

In summary, by following the methods set forth in the specification, one of skill in the art can select a detectable microorganism or cell for use in the method, including generation of recombinant microorganisms or cells, administer the microorganisms or cells to a subject, and detect the microorganisms or cells in the subject, thereby detecting a wound, wounded tissue, an inflammation site, inflamed tissue, or a disease or condition associated thereof. Thus, the specification teaches how to make and use the microorganisms or cells for the detection of wounded or inflamed tissues.

7. Existence of Working Examples

The specification provides working examples and descriptions of the generation, administration, and detection of microorganisms and cells for the detection of a wound, wounded tissue, an inflammation site or inflamed tissue. Such examples are valuable not only for the detection of the exemplified wounds and inflammation sites but for detection of any wound, wounded tissue, inflammation site, inflamed tissue, or diseases or conditions associated with wounds, wounded tissues, inflammation sites, or inflamed tissues.

The working examples of bacterial accumulation at wounded or inflamed sites provide sufficient teachings, in combination with what was known to those of skill in the art at the time of the instant application's earliest priority date, to generate, administer, and detect a microorganism or cell regardless of the microorganism or cell that is used provided that the microorganism or cell is detectable. For example, techniques for use in the administration and detection of luminescent bacteria in an animal model for wounded tissues are provided in Examples 1, 2 and 3, including examples of plasmid constructs that can be used for bacterial expression of bacterial luciferase, administration methods (e.g. intravenous injection), methods and equipment employed for detection, and methods for generating wounded tissue for the experiment, including incision wounds, ear tags wounds, and surgical heart defects. Such techniques are applicable to use of the methods in subjects with existing

wounds or inflamed tissues. Furthermore, the examples provide guidance for one of skill in the art to create animal models for testing particular detectable microorganisms and cells. For example, methods and instruction were provided for analysis of accumulation in wounded/inflamed tissue versus unaffected tissue in an animal model, including whole body luminescence detection as well as organ excision and cell culture methods for analyzing various tissues of the animal model.

Although the working examples exemplify the teaching using three species of bacteria (*S. typhimurium*, *V. cholera*, and *E. coli*), the teachings are directly applicable to any microorganism or cell, including viruses, bacteria, and mammalian cells, when placed in the context of the instant application in its entirety, which provides further guidance for the use of other microorganisms or cells, and the state of the art as discussed above. Further, Applicant is not required to provide data or illustrative examples in support of every assertion in the specification of everything within the scope of a broad claim. *In re Anderson*, 176 USPQ 331, at 333 (CCPA 1973)).

8. Quantity of Experimentation Needed to Make and/or Use the Invention

There is nothing of record to suggest that practice of the claimed methods would require excessive experimentation outside the scope of routine optimization of the methods. Preparation, generation, and administration of microorganisms and cells are routine manipulations that have been practiced for many years. Furthermore, detection techniques for *in vivo* detection and methods to optimize such techniques are also well-known. The application also provides ample guidance for routine testing of a microorganism or cell for use in diagnosis or treatment of wounded or inflamed tissues. Applicant notes that "a considerable amount of experimentation is permissible, if it is merely routine..." *In re Wands* 858 F.3d 731, 737.

a. Rebuttal to Examiner's argument that colonization is bacterial-strain dependent and administration dependent

On pages 13 and 14 of the Office Action, the Examiner alleges:

> Applicant has stated in the specification that even the bacteria used to infect the rats used have distinct interactions with the host cell (paragraph 0061), and the distribution pattern of any particular bacteria is not reasonably predictable, being bacterial-strain dependent (paragraph 0060) and moreover, the particular distribution patterns depends on the method of administration (paragraph 0045).

First, Applicant would like to make of record that the following two statements from the Office Action are statements made by the Examiner and not by the Applicant: "the distribution pattern of any particular bacteria is not reasonably predictable" and "the particular distribution patterns depends on the method of administration." Contrary to Examiner's assertion, neither statement was made by Applicant.

The Examiner has cited statements set forth in paragraphs [0060] and [0061] of the specification in support of the Examiner's argument that the distribution pattern of any particular bacteria is not reasonably predictable. To the contrary, the cited sections and accompanying working examples show that regardless of any differences in distribution profiles or kinetics, the tested microorganisms consistently localized at sites of inflammation, injury or disease.

The particular sections of paragraphs [0060] and [0061] of the specification that are set forth above reference statements taken out of context of the experiment described in Example 2. The statements describe the initial observation period only (0-60 minutes) for the experiment. As described in the specification, the experiment involves the injection of attenuated *Salmonella typhimurium* and attenuated *Vibrio cholerae* (each carrying the pLITE201 plasmid for expression of bacterial luciferase) into the left femoral vein of anesthetized mice. Prior to the injection, the left femoral vein was exposed by making a 1 cm incision with a surgical blade. Following injection of the bacteria, the incision was closed with 6-0 sutures, and the mice were then monitored under a low light imager for photon emission. The results for the initial distribution of the bacterial strains following injection into the mice were shown in Figure 1 of the application and described in Example 2. As stated in the paragraph [0060] of the specification:

> Injection of attenuated S. typhimurium caused wide dissemination of the bacteria throughout the body of the animals (FIG. 1A). This pattern of distribution was visible within 5 minutes after bacterial injection and continued to be detected at the one-hour observation period. Injection of attenuated V. cholera into the bloodstream, however, resulted in light emission that was localized to the liver within 5 minutes after bacterial injection and remained visible in the liver at the one-hour observation period (FIG. 1B).

The difference cited by the Examiner for localization of the two bacteria in this experiment refers to the initial observation period where *V. cholera* was seen to localize to the liver and S. *typhimurium* was more widely distributed throughout the animal. One of the

primary functions of the liver, widely known at the time of filing of the application, is to clear toxins and foreign materials from the bloodstream. It thus is not surprising that injected bacteria would accumulate in the liver soon after injection. Given what was widely known about the liver at the time of filing, one of skill in the art would not interpret this initial localization to the liver at five minutes post-injection of the bacteria to indicate that the liver is a site of a wound, wounded tissue, inflammation site or inflamed tissue. Regardless of any reasons why the bacterial strains may have differed in their accumulation in the liver during the initial observation period, this difference had no impact on the results of the experiment, in which both strains exhibited accumulation in the wounded and inflamed tissues after clearance of the initial wave of distribution as shown in Figure 2.

It respectfully is submitted that the statement in paragraph [0061] that "the distribution pattern of light emission following an intravenous injection of bacteria into the mice was bacterial-strain-dependent" should not be taken out of context of the experiment as a whole. The statement refers only to the initial observation period of the experiment and has no bearing on the outcome, namely, both bacterial strains accumulated in the wounded/inflamed tissues and not in uninjured tissues. This was clearly shown in Figure 2 as well as stated in paragraph [0061]:

> Imaging the same animals 48 h after bacterial injection showed that **all** of the detectable light emission from the earlier time had diminished and was eliminated completely from the injected animal with the exception of the inflamed wounded tissues such as the incision wound and the ear tag region...Careful examination of individually excised organs as well as blood samples from infected animals confirmed the absence of luminescence in these normal uninjured tissues."[emphasis added].

Hence, the Examiner's assertion regarding the difference in the distribution among the bacterial strains has no bearing on the ability of both tested strains to accumulate in wound/inflamed tissues, as supported by the Examples.

With respect to paragraph [0045] mentioned above, the Examiner asserts that "the particular distribution patterns depends on the method of administration." No such admission is made by Applicant. Paragraph [0045] of the specification teaches that the microorganisms or cells can be administered using different routes "e.g. by intravenous, intraperetoneal, subcutaneous, intramuscular, topical or intradermal administration." Applicant states in paragraph [0045] that:

> The route of administration, of course, depends on the nature of the tissue and the kind of microorganisms or cells contained in the pharmaceutical composition. The dosage regimen will be determined by the attending physician and other clinical factors. As is well known in the medical arts, dosages for any one patient depends on many factors, including the patient's size, body surface area, age, sex, the particular compound to be administered, time and route of administration, the kind and localisation of the tissue, general health and other drugs being administered concurrently.

Although the route of administration can depend on the kind of microorganisms or cells contained in the pharmaceutical composition, the cited passage clearly teaches that selection of an appropriate route is a matter of routine, given the advanced state of the art with respect to administering microorganisms or cells to subjects. The cited passage in no way implies that the route of administration would affect the ability of the microorganisms or cells to localize to wounded, diseased or inflamed sites as taught by the methods of the specification. Instead, the specification merely states that particular routes of administration may be better suited for detection of a particular wounded or inflamed tissue. As discussed above, factors for determining the preferred route of administration based on the type of wound or inflamed tissue are taught by the specification and are known to those of skill in the art. Furthermore, as discussed above, one of skill in the art would possess the knowledge needed for assessing such factors for determination of an administration route and dosage.

b. Rebuttal to Examiner's assertion that initial accumulation in the liver falsely indicates a wounded or inflamed tissue

On page 14 of the Office Action, the Examiner states that "by Applicant's method, if a rat was unaffected, accumulation in the liver would indicate that the liver had a wound, inflammation, and coronary artery disease." This is incorrect. As argued above, one of skill in the art would be aware of the function of the liver to cleanse foreign matter from the bloodstream. As such, if the bacteria were administered such that the bacteria were deposited into or had access to the blood stream (e.g. by intravenous administration), it would not be surprising to observe accumulation in the liver. Hence, one of skill in the art would not interpret this initial accumulation in the liver as an indication of a wounded or inflamed tissue.

Furthermore, the specification teaches the kinetics of targeting and clearance of the microorganisms from the non-wounded or non-inflamed tissues. Thus, one of skill in the art

would be able to distinguish whether the accumulation of the microorganisms or cells is the result of toxic clearance or accumulation at a wounded or inflamed tissue.

c. Rebuttal to Examiner's assertion regarding accuracy of the method

The Examiner argues that the method is accurate "at best, only 41.4% of the time (paragraph 0061)" and that "Applicant may argue that 82.8% of the injection wounds also showed such colonization, but such may also be explained by the fact that such is where the bacteria was present in high concentration, and hence, it would not be reasonably predictable for non-injection wounds, and therefore would require undue experimentation for the breadth to make it so-predictable."

Applicant respectfully disagrees with the Examiner's conclusion and interpretation of the experiment presented in Example 2. The Examiner has failed to take into account that the bacteria were widely dispersed throughout the animal or found in the liver and not at the inject site immediately following injection (as shown in Figure 2 and Figure 3). As such, there was not a disproportionate concentration of bacteria at the injection site at time points soon after injection. The accumulation of light emitting bacteria at the site of incision was gradual and accompanied by complete disappearance of the light emitting bacteria from sites other than the wounded/inflamed tissue after 2 days. Although the percentage of bacterial wound colonization was less at the sites of ear tag wounds (41.1%), the colonization that did occur was clearly detectable over non-wounded/inflamed tissues. The lower colonization may simply reflect a difference in the level of inflammation at the site of the individual ear tags. As such, the lower colonization cannot be a reflection of the accuracy of the method as asserted by the Examiner. In fact, the result that the bacteria did not accumulate in non-wounded or non-inflamed tissues following the initial observation period for both strains tested further demonstrates the success of the method.

Notwithstanding the arguments above, Applicant respectfully submits that a particular level of efficacy is not required to demonstrate that the method is enabled. Methods of optimizing a regimen to achieve higher colonization levels for a particular microorganism or cell would not be considered undue experimentation. Further, the Examples demonstrate that by following the teachings of the specification one of skill in the art can use the method to administer a microorganism or cell to a subject with a wound or inflamed tissue and can

detect accumulation of a microorganism or cell at a wounded or inflamed tissue without undue experimentation.

d. Rebuttal to Examiner's argument regarding enablement of the detection techniques encompassed by the claims

The Examiner asserts:

> the specification only discloses fluorescent proteins, for detection by light emission, and by MRI.. However, Applicant's claims encompass any detection method. However, given that Applicant wishes to detect these tissues, the method would not be one which causes any damage to the organism itself, because, according to the method, the microorganism/cell would accumulate in the damaged tissue, and provide false readings, it would appear that the only methods of detection are by MRI or fluorescence detection.

It respectfully is submitted that the Examiner is required to do more than just categorically state that some of the detection methods "may" damage tissues. Judicial notice cannot be taken unless the facts are capable of "instant and unquestionable demonstration."

The Examiner is reminded that MPEP 2144.03 states:

> The Examiner may take official notice of facts outside of the record which are capable of instant and unquestionable demonstration as being "well-known" in the art. In re Ahlert, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970). . . ..

In this instance, it is not "unquestionably demonstrable" that detection techniques for visualizing tissues, damage tissues. To the contrary, detection techniques to visualize tissues are selected not to damage tissues, as the end result of visualizing the tissues would then not be achieved. The Examiner therefore is required to provide documentary evidence that such tissue damage occurs.

Further, Applicant's methods are premised on using microorganisms and cells to detect and treat localized wounds, diseases or sites or inflammation, not to damage the target sites. The non-pathogenic or attenuated microorganisms taught by the specification are designed for this purpose and the teachings of the specification, when combined with the advanced knowledge of those of skill in the art, would allow one of skill in the art to select suitable methods of detection and suitable microorganisms or cells to perform the methods as claimed, without damaging tissues. Furthermore, the detection methods taught by the specification are well known as non-damaging methods for imaging tissues. Inherent to the purpose of a detection method to image or visualize tissues, is that the tissues not be

damaged. The state of the art at the time the instant application was filed, and as of its earliest priority date, was advanced in the knowledge of how to detect/image tissues without damaging them. The specification teaches the use of these known detection methods in conjunction with the microorganisms or cells used in the claimed methods. The application is directed to the "honing microorganisms or cells" and their use in detection or treatment methods, not to detection techniques (such as MRI, fluorescence, etc.), which already were known in the art and are taught by the specification for use with these methods.

Furthermore, Applicant respectfully disagrees with the Examiner's assertion that the only methods of detection of the microorganisms or cells taught by the specification are by MRI or fluorescence detection. Restriction to these two methods of detection is unduly limiting for the practice of the claimed methods.

Of note, Examiner's statement that "the specification only discloses fluorescent proteins, for detection by light emission, and by MRI" is incorrect. The specification discloses many examples of proteins that can be used for detection in the claimed method that are not fluorescent proteins. For example, the specification discloses various luminescent proteins, such as bioluminescent proteins (e.g., luciferases), which are not fluorescent proteins. By definition, a fluorescent protein requires incident light in order to fluoresce or emit light, whereas a luciferase catalyzes the oxidation of a substrate molecule in order to emit light. Further, the bacterial strains employed in the Examples contain a luxcdabe cassette which allows for the expression of a bacterial luciferase.

The specification also provides additional examples of detection including use of a metal binding proteins or proteins that can bind a contrasting agent, chromophore, or a compounds. One of skill in the art at the time of filing of the instant application, and as of its earliest priority date, would understand that a compound that binds to protein can be, for example, a radiolabeled compound or a compound that contains a paramagnetic ion, or produces ultrasound echoes. As such, the compound when bound to the microorganism or cell, can be detected by a variety of methods known to those of skill in the art as of the application's earliest priority date including magnetic resonance imaging (MRI), positron emission tomography (PET), single photon emission tomography (SPECT), X-ray computed tomography (CT), ultrasound. Examples of such compound and detection methods were all available and known to one of skill in the art at the time of filing and as of the earliest priority date.

Summary

In summary, as discussed above, to demonstrate the full scope of enablement of the claimed methods, Applicant is not required to demonstrate a completely optimized procedure as long as it is possible to successfully carry out each of the steps of the method with reasonable, but not undue experimentation. Contrary to the assertion of the Office Action, the ability to practice the methods as claimed is not dependent on the particular microorganism or cell that is used in the method. Instead the non-pathogenic or attenuated microorganism or cell is a tool that is used to detect abnormal conditions in a subject, such a wound or inflamed tissue, a foreign object (e.g., a suture), or a disease or condition associated with wounded or inflamed tissue. It is not a characteristic of the particular microorganism or cell per se that provides for specific colonization of the wounded or inflamed tissue, but rather the protective environment of the wounded or inflamed tissue that permits colonization of such site by microorganisms and cells which are cleared by the immune system from other non-wounded or non-inflamed tissues. Hence, any microorganism or cell that is recognized by the immune system should have the ability to accumulate in wounded or inflamed tissue as taught by the specification. The claimed methods are thus broadly applicable to any non-pathogenic or attenuated microorganism or cell.

It is respectfully submitted that in providing a case for rejection based on enablement, that Examiner has not specifically identified what information is missing or why one skilled in the art could not supply the information without undue experimentation. The Examiner simply has provided no basis for the conclusion that one of ordinary skill in the art would not have been able to use the claimed method. The Examiner has stated on page 13 of the Office Action that "the Artisan would not reasonably predict that any microorganism or cell would accumulate in any of the tissues claimed." However, the examiner does not put forth any concrete examples in the Art that would suggest otherwise or that would suggest the art is unpredictable. Instead, the Examiner has relied on an unsupported opinion that any microorganism or cell would not accumulate in a wound or inflamed tissue. Given the teachings of the specification and the working Examples provided, Applicant has provided evidence that any microorganism or cell would be predicted to accumulate in a wounded or inflamed tissue.

Further, on page 9 of the Office Action, the Examiner states, "Because of the art, as shown above, does not disclose enough to reasonably predict the working embodiments

encompassed by Applicant's claim, the Artisan could not predict, in the absence of proof to the contrary, that such applications would [be] efficacious in any diagnosis." Examiner makes reference to "art, as shown above"; however, no art was shown other than Yu et al., therefore it is unclear as to which art the Examiner is referring. With regard to efficacy for diagnosis, the Examiner again appears to set forth an argument for inoperability of the claimed method where no such rejection has been set forth in the Office Action. Hence, the Examiner has not provided any indication of what disclosure is absent from the application that provided basis for the lack of enablement.

Further, in order to practice the methods as claimed, it not required that a particular microorganism or cell achieve a minimum level of colonization at the site of the wounded or inflamed tissue as suggested by the Examiner on page 14 of the Office Action. It is respectfully submitted that the Examiner is equating the standard for enablement of the claimed subject matter with an established clinical gene therapy regimen. Such is not the standard for enablement or operability. (See, e.g., MPEP §2164.05, Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) for the proposition that considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled. *See also*, for example, MPEP §2107.03, In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995) holding that FDA approval is not a prerequisite for finding utility within the meaning of the patent laws).

Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy in order for a treatment-related area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. §112, first paragraph, is not a consideration. The relevant standard is not that of an established, fully optimized, clinical course of treatment; rather, even in an unpredictable art, a patent application satisfies the requirements of 35 U.S.C. §112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation. There is no requirement that a method achieve a specified level of efficacy or efficiency in order to be considered "enabled" by the specification.

It appears that the Office Action, in asserting the unpredictability of the claimed methods, has equated a fully established clinical or experimental regimen, uniformly applicable across every system, with "unpredictability." It is respectfully submitted that, as

the references of record establish, microorganism or cells other than those used in the Examples provided in the application, can be administered to a subject, and, as further evidence by the disclosure of the application, detection of accumulation at a site of wounded or inflamed tissues can be achieved successfully. The level of success does not have to be absolute to establish the art as predictable. The practitioner is well aware of the potential obstacles and clearly knows what he or she is up against in designing and carrying out such methods. As such, it is respectfully submitted, that although the art of the use of microorganisms or cells for the purpose of detection or treatment of wounded or inflamed tissues may not have been a routine, clinical practice at the effective filing date of the subject application, it was not so unpredictable as to qualify as a major factor in the determination of whether the requirements of 35 U.S.C. §112, first paragraph, are satisfied with respect to the instantly claimed subject matter.

Policy Considerations

A significant portion of the grounds for the rejection of the claims under 35 U.S.C. §112, first paragraph, is based on the alleged unpredictability of the use of microorganisms and cells for the detection of wounded and inflamed tissues.

First, as discussed above, enablement does not require demonstration of every embodiment of a method, nor of a fully perfected, optimized method, nor of every use of every method as claimed. It is required only that any amount of experimentation used by one of skill in the art in making and using the claimed subject matter not be undue. Further, the Examiner has not cited any references to suggest that the experimentation needed to perfect the technique would not simply be routine. It is respectfully submitted that the guidance provided in the Art with regard to the administration of microorganisms or cells to subjects and detecting their accumulation in tissues is sufficient for one of skill in the art to carry out the steps of the method in a predictable fashion, with routine modifications to apply the method using any microorganism or cell.

As demonstrated by the above analysis of the *In re Wands* factors, the teachings of the specification, when combined with the knowledge of those of skill in the art and the ability to repeatedly and successfully (i.e., predictably) execute the various steps, leads to the conclusion that each of the steps of the instant methods could be performed without undue experimentation. As discussed above, administration of microorganisms for the detection of wounded or inflamed tissue was successfully demonstrated using a variety of microorganisms

by following the teachings of the instant application and by an extensive body of knowledge in the art as of the application's earliest priority date.

Applicant is entitled to claims that are commensurate in scope not only with what Applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the Applicant has disclosed. In the instant application, Applicant provides the public with methods and compositions for the detection of a wound, wounded tissue, an inflammation site, inflamed tissue, or a disease or condition associated thereof by administering and detecting a variety of microorganisms or cells that accumulate at such sites for the purposes of diagnosis and treatment. As a broad body of knowledge is available in the areas of microbiology, genetic manipulation of microorganisms and cells, administration of microorganisms and cells to subjects, and *in vivo* detection techniques for detecting the administered microorganisms and cells, it would be unfair and contrary to the Constitutional mandate set forth in Article, Section 8, to deprive Applicants of protection of the broad applications of the pioneering discovery disclosed and described in exhaustive detail in the subject application.

See, e.g., In re Goffe, 542 F.2d 801, 166 USPQ 85 (CCPA 1970).

> The public purpose on which the patent law rests requires the granting of claims commensurate in scope with the invention disclosed. This requires as much the granting of broad claims on broad inventions as it does the granting of more specific claims on more specific inventions" In re Sus and Schafer, 49 CCPA 1301, 306 F.2d 494, 134 USPQ 301, at 304.

VII. REJECTION OF CLAIMS 33-34, 36-37, 42-43, 57-62, AND 69-72 UNDER 35 U.S.C. §102(b)

Claims 33-34, 36-37, 42-43, 57-62, AND 69-72 are rejected under 35 U.S.C. § 102(b) as anticipated by Pace (JAMA, 284(22):2964 (2000)) because Pace allegedly discloses detection of an inflamed tissue, in this case inflamed throat tissue caused by *Streptococcal* infection of the throat, by visual diagnosis of the throat and detection of administered bacteria by throat culture. This rejection is respectfully traversed.

Relevant Law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. *In re Spada*, 15 USPQ2d 1655 (Fed. Cir, 1990), *In re Bond*, 15 USPQ 1566 (Fed. Cir. 1990), *Soundscriber Corp. v. U.S.*, 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, *Richardson v. Suzuki Motor Co.*, 868

F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention." *In re Lang*, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). It is incumbent on Examiner to identify wherein each and every facet of the claimed invention is disclosed in the reference. *Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co.*, 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984). Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. An inherent property has to flow naturally from what is taught in a reference. *In re Oelrich*, 666 F.2d 578, 581, 212 USPQ 323, 326 (CCPA 1981).

"Rejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the 'prior art' . . . the [r]eference must clearly and unequivocally disclose the claimed compound or direct those skilled in the art to the compound without *any* need for picking, choosing, and combining various disclosures not directly related to each other by the teachings in the cited references. Such picking and choosing may be entirely proper when making a rejection of a §103, obviousness rejection, where the applicant must be afforded an opportunity to rebut with objective evidence any inference of obviousness which may arise from the *similarity* of the subject matter which he claims to the prior art, but it has no place in the making of a §102, anticipation rejection." (Emphasis in original). *In re Arkey, Eardly, and Long*, 455 F.2d 586, 172 USPQ 524 (CCPA, 1972).

The Claims

Claim 33 and claim 34 are directed to a method of detecting the presence or absence of a wound or wound tissue (claim 33) or inflammation site or inflamed tissue (claim 34) comprising administering a non-pathogenic or attenuated microorganism or cell that is recognized by the immune system to a subject, and then detecting the microorganism or cell in the subject, thereby detecting the presence or absence of a wound or wound tissue (claim 33) or inflammation site or inflamed tissue (claim 34). Claims 36-37, 42-43, 57-62, and 69-72 ultimately depend from either claim 33 or 34 and are directed to various embodiments thereof.

Disclosure of Pace

Pace discloses that *Streptococcus* bacteria that have infected throat tissue can be detected by a throat culture and the inflamed tissues caused by the *Streptococcus* infection can be detected by direct visualization of the throat tissues. Pace does not disclose that

microorganisms or cells are administered for detection of a wound, wounded tissue, an inflammation site, or inflammation.

Analysis

Pace does not anticipate the claimed subject matter for the following reasons:

1. Bacteria disclosed in Pace are not administered for detection

The method recited in claims 33 and 34 comprises "monitoring a subject to whom a detectable microorganism or has been administered for detection of the microorganism or cell.." The claims explicitly state that the microorganism or cell has been administered for detection. Pace does not disclose such microorganism or cell. First, the *Streptococcus* bacteria disclosed in Pace that have colonized the throat of the subject were not *administered* to a subject, Instead, the *Streptococcus* bacteria infected the subject in the absence of an administration step. Examiner may argue that infection by *Streptococcus* bacteria is a form of administration. Applicant respectfully disagrees. The term "administration" implies a managed or supervised application of the microorganism or cell. Furthermore, the term should be defined in view of the disclosure in the specification of the instant application, which discloses that the microorganisms or cells are administered via suitable method. For example, in paragraph [0045], the Applicant states, "Administration of the microorganisms or cells may be effected by different ways, e.g. by intravenous, intraperetoneal, subcutaneous, intramuscular, topical or intradermal administration." Chance infection or existing infection is not included or implied for administration. Based on the disclosure of the Application, including the Examples which demonstrate intravenous administration of the microorganisms or cells, one would conclude that administration of a microorganism or cell is a managed act. Secondly, even if the infection by *Streptococcus* bacteria disclosed in Pace were interpreted to be an administration event, the method disclosed by Pace still does not anticipate the methods claimed in claim 33 and 34 since the *Streptococcus* bacteria was not administered for the purpose of detection. Claim 33 and claim 34 explicitly state that the detectable microorganism or has been administered for detection of the microorganism or cell. The *Streptococcus* bacteria of Pace was not administered for detection. Hence, Pace does not anticipate claim 33 or claim 34, nor any dependent claim dependent thereon.

2. Pace recites two separate detection steps

In addition, it was noted in the Office Action on pages 5-6 the Examiner has interpreted claims 33 and 34 to encompass two detection steps "in which bacterial cells are

administered and detected, then a tissue commensurate with the scope is detected." As addressed above, Applicant respectfully submits that this is incorrect. The specification discloses that the microorganisms or cells are administered and then detected, *thereby* detecting the wounded or inflamed tissue. Without concurring with the Examiner's interpretation and in the interest of clarifying the method, Applicant has amended claims herein to recite that the method of claim 33 comprises "detecting the presence or absence of the detectable microorganism or cell, thereby detecting the presence or absence of a wound or wounded tissue" and the method of claim 34 comprises "detecting the presence or absence of the detectable microorganism or cell, thereby detecting the presence or absence of an inflammation site or inflamed tissue." In light of these amendments, it is furthermore demonstrated that the disclosure of Pace does not anticipate the claims at issue. Pace discloses detecting the inflamed tissue by visual diagnosis, then detects the bacteria by throat culture. In contrast, the claimed method of claims 33 and 34 recite detecting the microorganism or cell, thereby detecting the wounded or inflamed tissue. Pace does not disclose this method. Hence, Pace does not anticipate claim 33 or claim 34, nor any dependent claim dependent thereon.

3. *Streptococcus* bacteria of Pace are not non-pathogenic or attenuated

Finally, as discussed above, claims 33 and 34 have also been amended herein to recite that the microorganism or cell that is administered is a "non-pathogenic or attenuated" microorganism or cell. As such, the *Streptococcus* bacteria of Pace are not encompassed within these claims since it is a pathogenic strain of *Streptococcus* bacteria that is disclosed in Pace. Pace does not disclose this element of claim 33 or claim 34, thus Pace does not anticipate claim 33 or claim 34, nor any dependent claim dependent thereon.

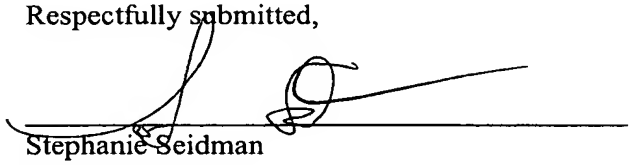
Conclusion

Applicant respectfully submits that merely monitoring a subject that has a bacterial infection and inflamed tissue as a result of the infection does not anticipate the claimed method of administering a detectable microorganism or cell for detecting an inflamed or wounded tissue. In the claimed method, the microorganism or cell is administered for the purposes of detecting the tissue (i.e. it allows detection). Pace does not such a method. Furthermore, in view of the arguments and amendments set forth above, it is submitted that Pace does not disclose each element of the claims under consideration. Therefore, Pace does not anticipate claim 33 or claim 34, nor any dependent claim dependent thereon.

* * *

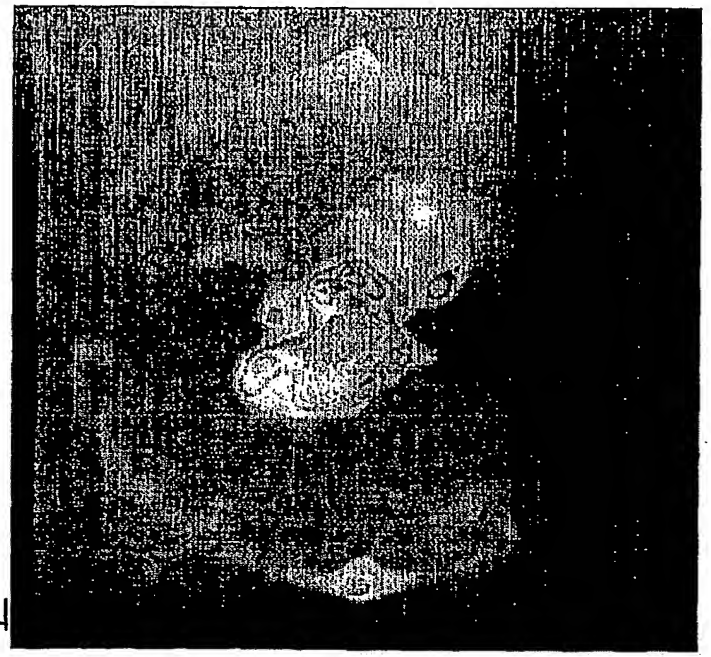
In view of the above, reconsideration and allowance of the application are respectfully requested.

Respectfully submitted,

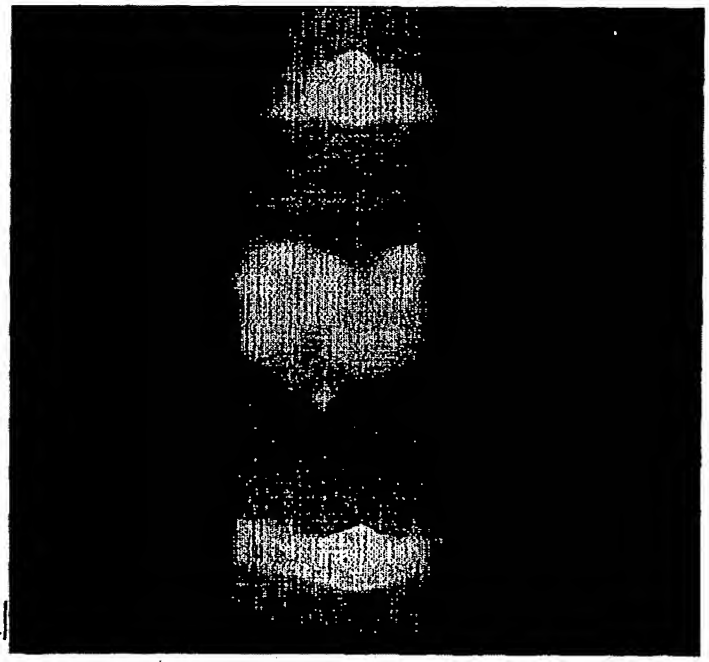


Stephanie Seidman
Reg. No. 33,779

Attorney Docket No. 17248-004002/4804B
Address all correspondence to:
Stephanie L. Seidman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, California 92130
Telephone: (858) 678-5070
Facsimile: (202) 626-7796
email: seidman@fr.com



B



A

Figure 6